minimize any changes in intracranial pressure; and all of the other measures that pertain to nursing care.

Then during re-warming, there's this afterdrop which causes an unexpected shift in temperature as the cooling blood goes to the extremities, and at the end of the maintenance phase, patients can get hypotensive, so you need to give them a little bit of volume before you re-warm them. And as potassium shifts back, you can get hyperkalemia, so you want to stop any potassium supplementation as you prepare to re-warm, and then slowly allow the patient to re-warm.

We try not to go any more than one degree every four hours, but as you'll find when I show you the data, it's hard to control the re-warming phase. And then you have to support perfusion pressure during the warming phase.

Okay. Now, with those introductory comments, let's talk about the particular indications that are being discussed. First of all, we did a small trial of hypothermia in cardiac arrest. Larger trials are now underway and should be reported soon. But I think the data that we've obtained are instructive, and I should point out that Dr. Krieger, when he was in Houston, was instrumental in the design of this protocol.

So first just some demographics. We've heard a lot about stroke, but it's important to know that there's 62

cardiac arrests for every 100,000 people in this country each year, and it's a devastating condition. Out of 3,243 cardiac arrests in New York City--this was reported in 1994, but it's representative--349 had a return of spontaneous circulation, that is, were successfully resuscitated. These were out-of-hospital cardiac arrests. And only 26 were discharged from the hospital alive. Now, this was before the advent of AEDs, or automatic external defibrillators, which are improving these statistics. But, still, a very small proportion of patients with out-of-hospital cardiac arrests are discharged alive, and no treatment exists for the hypoxic encephalopathy that occurs as a result of cardiac arrest.

So, in our trial, patients had to have confirmed out-of-hospital cardiac arrest. They had to have return of spontaneous circulation within 60 minutes of the initiation of advanced cardiac life support. Now, in most cases, ROSC, or return of spontaneous circulation, was defined as an unsupported systolic blood pressure of 90. So they had to be resuscitated to a systolic blood pressure of 90 within 60 minutes of initiating ACLS. And if they didn't do that, then obviously they--you'll notice that there's no measure of downtime, of how long the patient was down before ACLS was started, because that's a notoriously difficult interval to determine. But if patients were down for a prolonged

period of time, they are not going to get return of spontaneous circulation within 60 minutes. So this is sort of a surrogate marker for downtime, and it is frequently used in these trials.

Then we had to start hypothermia within 90 minutes of the time ACLS was started in the field, so the paramedics had to start ACLS, and rather than treating the patient in the field with all sorts of things, they moved them to the hospital fast so that we could get consent and hypothermia started within 90 minutes. And in this study, we did have to get informed consent, and I'll come back to that in a minute. Patients all had to be comatose with a Glasgow Coma Scale of 8 or less to go into this trial.

They were immediately sedated with propofol and paralyzed. We did the ice bags, iced saline lavage, and then we wrapped the patient, barrel-rolled them into two cooling blankets, and maintained them at 33 degrees for 24 hours. And then we passively re-warmed at one degree every four hours, and we stopped paralytics and sedation when the patients got up to 35 to 36 degrees.

We enrolled--just to give you an idea of how many patients can be enrolled, in the course of a little over a year, we enrolled nine patients at this center, six men and three women, and seven of them were due to premature ventricular fibrillation arrest. One patient was a woman

who walked into a building in the morning where she worked where a carbon dioxide tank had leaked overnight and she was asphyxiated. And another patient had sudden unexpected death from epilepsy.

In the emergency room, their average temperature was 36 degrees, and I'll show you in a minute that there's an interesting dichotomy that may relate to outcome. Many patients come in hypothermic, and you can see that their temperature range in the emergency room was between an already hypothermic 33 degrees and 37 degrees. Average Glasgow Coma Scale was 3.6. Most of these patients actually had fixed, dilated pupils, and remember, most neurologists are taught that when a patient comes into the emergency room and is fixed and dilated, it's pretty hopeless. I'll show you that's not true.

The average time from cardiac arrest to return of spontaneous circulation was 24 minutes, so most of these patients were resuscitated to a systolic pressure of 90 within 24 minutes. The longest was 35 minutes. And they were started, on average, to hypothermia from the onset of cardiac arrest at about 91 minutes. But then it took six hours, six and a half hours, on average, for them to achieve--from the onset of cardiac arrest to achieve the target temperature. So it was about four and a half hours on average from the time we started hypothermia to the time

we obtained the target temperature, or six hours from the time the patient arrested.

Of the nine patients we enrolled, four patients survived, three of whom completely returned to baseline functioning and walked out of the hospital. One had some modest memory deficit, and then five patients died.

We reviewed all the cardiac arrests in our hospital during the same period of time, and of those 156 total cardiac arrests, 110 of them were out-of-hospital cardiac arrests; 13 of them had return of spontaneous circulation but did not qualify for the study, and there were no survivors among those. And of the six patients who qualified for the study but were to included, mainly because they didn't sign consent, there were no survivors. So that's whatever comparison data that we have.

Complications. We had five cases of pneumonia that were mild and easily treated; four cases of status epilepticus, all in patients who ultimately died; four patients had elevated lipase or amylase; three patients had some mild electrolyte abnormalities; three cases of mild azotemia; one mild coagulopathy and one ventricular tachycardia. So, generally, even though these seem like a lot, these are the typical sorts of things you see in cardiac arrest patients who are resuscitated, except for-- even some of these amylase elevations. Certainly seizure

are very common. So we weren't sure that this was any more common than what we would see in patients who otherwise had anoxic brain injury.

This was not a randomized trial, and obviously we may have enrolled healthier patients to this trial than what normally are seen. Other limitations were that hypothermia was not achieved quickly and the re-warming was not well controlled. I didn't point this out, but we had overshoot in a large number of the patients as we re-warmed them. And one of the questions comes up, the main reason why we could not enroll patients who otherwise qualified was because we could not obtain consent. So for these out-of-hospital arrest trials, if we're going to do trials in cardiac arrest, we should consider waiver of consent, as was used in the head trauma trials.

So my recommendations for cardiac arrest trials, we need a better method for achieving and maintaining hypothermia and re-warming, and that will be a consistent message for all of the indications that I'll discuss. The variability in outcome demands that we randomize patients and not use natural history controls. This is a changing landscape now in cardiac arrest with external defibrillators, and I don't think we can rely on historical controls in cardiac arrest studies. I think we should consider waiver of consent. I think we can--we thought that

we would only do out-of-hospital arrests because we felt like patients with in-hospital arrests would be too sick. And, in fact, I don't think that's the case. We found very few complications of 24 hours of hypothermia. I think we could do in-hospital arrests, and I think we also could include patients with myocardial infarctions.

Patients who came in who clearly had had an MI associated with their arrest were excluded because we were afraid of cardiac arrhythmias. But we only had one case of ventricular fibrillation, and most of our cardiac colleagues feel that we could safely enroll patients who had even documented acute MIs associated with their cardiac arrests.

I think we should keep patients at 33 degrees for 24 hours, although I could hear arguments for maybe a little longer, but I don't think it's necessary to keep them any longer than 24 hours because I think you start buying side effects that probably aren't warranted. And I think it's very important to measure as outcomes survival and, of course, cognition. Cognition among survivors is very variable. They don't have focal deficits as much as they do have memory deficits. And I think one-month outcome measure is probably adequate for a cardiac arrest trial. And secondary measures that need to be looked at are the ability to control temperature in re-warming, the incidence of infection, and arrhythmias.

Okay. That's all I want to say about cardiac arrest. We've already heard a lot about stroke. Let me just mention two studies in the literature, one by Schwab and colleagues in Stroke, which Dr. Krieger and Dr. De Georgia alluded to. This study, the purpose of this was to control cerebral--was not really to treat the ischemic penumbra itself but, rather, to control the edema in patients who had very severe middle cerebral artery stroke with mean NIH Stroke Scale score of 24, the lowest being 18, very severe strokes. Cooling was not started until, on average, 14 hours after the stroke. It used cooling blankets to 33 degrees with paralysis, the same as we used, for all intents and purposes, in the cardiac arrest trial. They also took three and a half to six hours to achieve cooling, just as we did in our cardiac arrest trial. They kept patients cool for two to three days.

They did find that ICP was reduced in this trial significantly, and as complications, there was some reduction in heart rate, platelet count, and potassium, and some increased lipase. But the important point was they felt like they were able to control severe cerebral edema in these devastated, malignant middle cerebral artery patients.

Of perhaps more interest to the general stroke population and the practical applicability is this trial by Kammersgaard et al. that I remember reading and Dr. Krieger

reminded me about, published this last year in Stroke, where they used a forced air Bair Hugger for six hours as sort of a forced air method to cool the patient, and cooled them only down to 35 degrees. Remember I showed that in preclinical models, cooling just to 35 degrees is somewhat neuroprotective. They were able to accomplish this in 17 patients within 12 hours of onset and to control shivering just with low doses of pefidine (ph), which I think is Demerol in this country, and I think it remains--and you can see this is the temperature curve, a gradual reduction over the first six hours to the target temperature. And the point is that particularly if we're going to couple this with other approaches such as thrombolysis or neuroprotection, these modest degrees of hypothermia may be tolerable in all stroke patients, or certainly anybody with a significant deficit, not just in patients who are getting thrombolysis or who have malignant middle cerebral artery syndrome.

So for future stroke trials, I think the preclinical data would indicate that hypothermia must be achieved fast. This is perhaps something that could be started pre-hospital, in the ambulance. Our paramedics--we're training a whole cadre of paramedics in our cities where there are stroke centers to recognize stroke patients and to get them to the hospital fast. If hypothermia proves

to be useful, this would seem to be a therapy that could be started in anybody with suspected stroke early on, at least in terms of ice bags and gavage.

It should be maintained throughout the reperfusion phase, probably for at least 24 hours into reperfusion, as I pointed out from the preclinical data. I don't know what is the--I think if it's a severe stroke and the patient's got to be on a ventilator, such as a malignant middle cerebral artery syndrome, then reducing the temperature to 33 degrees to control edema is logical. But in the less severe affected patients, the 35 degree target is also logical and more applicable to larger numbers of patients.

And then I think as in other stroke studies, as Dr. Zivin pointed out, we need to measure outcome at three months and measure survival and disability.

Okay. We've heard a lot about head trauma. I'd like to show you some data that was given to me by Dr. Clifton at our center from the head trauma trial, a multi-center trial that you know was carried out in a number of centers, and these data have been presented.

The purpose of this trial was to determine if surface-induced--using cooling blankets--hypothermia to 33 degrees begun within six hours of closed head injury and maintained for 48 hours improved outcome without toxicity.

Patients had to be between 16 and 65 years of age,

Glasgow Coma Scale of 3 to 8, comatose, with non-penetrating injury to the head.

They had to be able to initiate cooling within six hours. Glasgow Coma Scale of 3 or bilaterally unreactive pupils excluded patients. And if they were significantly hypotensive, had bleeding problems, pregnancy, or other severe medical conditions, they were excluded.

Now, let's look at a few things that are important from this trial. First of all, patients in the hypothermic group here on the left compared to the normothermic group required more fluids. They required three liters of fluid as opposed to 1,947 on average. That was a significant difference. They needed--a higher percentage of those patients required some vasopressors to support their blood pressure, and more hours on vasopressors, and they had slightly more complication days than did patients who were normothermic.

Unfortunately, there was no effect on outcome. The percentage of patients with poor outcome in the hypothermic group or the normothermic group was no different whether you looked at all patients, those was Glasgow Coma Scale on admission of 3 or 4 or those 5 through 8, and the mortality also was not significantly different.

There was a significant reduction in intracranial pressure, as was seen with the malignant cerebral artery

trial, the hypothermic patients having lower intracranial pressure than the normothermic patients. But they were able, with appropriate pressors and whatever, to make sure that there was no difference in mean arterial pressure or in perfusion pressure between the two groups. So any differences could not be attributed to these variables.

Now, there did seem in post hoc analysis to be some interesting relationships that might be hypothesis-generating for future trials. If you look at those patients who came in hypothermic with temperatures less than 35, there did appear to be a trend towards better outcome in patients who were hypothermic. So, in other words, if they already were hypothermic and you kept them hypothermic, they had less poor outcome, and this was particularly true in patients with more severe--younger patients with more severe injury: 52 percent poor outcome compared to 76 percent for patients under 45 with Glasgow Coma Scale of 3 to 8. I'll come back to that in a minute.

In patients whose admission temperature was greater than 35 degrees, there was no significant difference, and the issue would be that these patients were not hypothermic during the initial phase of their injury when it was most important. And so maybe the hypothermia was not obtained fast enough in these patients, and those patients who came in hypothermic who were hypothermic right

from the beginning of their injury or soon thereafter, sort of on their own, that they had some beneficial effect.

This shows the typical curve of what was achieved in patients who came in with low admission temperatures. You can see this is their temperature. They went up a little bit, actually, in the first hour or so. They tended to warm up as soon as they arrived, but then were cooled down compared to those who came in with admission temperatures over 35 degrees, and then they all were about the same after the first ten hours. So this is why--one of the hypotheses for explaining the results is that patients simply weren't cooled fast enough in this group.

This shows the temperature data over the entire period of hypothermia. You can see they successfully were able to get the temperature down and keep it down, but it did take eight hours or so, 8.4 hours to achieve the target temperature on average from the time of injury, which probably is too long.

So for head injury, I think there probably is room for another trial, but the question would be to tailor it to patients who come in who already are hypothermic who are younger and who have low Glasgow Coma Scales, and try to target their temperature within five hours of their injury. Intracranial pressure, perfusion pressure, and fluids need to be monitored carefully. And in these patients, outcome

needs to be measured out to six months. It takes quite a while for these patients to improve their level of consciousness and functional outcomes, so in these head trauma trials, I think the outcome needs to be measured later on.

We've already heard about aneurysm surgery. I was able to find--of course, this abstract wasn't privy to the data that was already presented, so I won't go over it in detail. But as you've already heard, patients were reduced to 33.5 degrees intraoperatively using forced air. Interestingly, seven patients could not be cooled because they were obese as the main factor, and I think that that limits the applicability in overweight patients with subarachnoid hemorrhage. And there was--in those patients who had ruptured aneurysms, as was pointed out by the previous speakers, a non-significant trend towards less neurological deterioration and better long-term outcome.

So, in conclusion, hypothermia consistently and potently reduces damage after experimental cerebral ischemia and head trauma. I think in all of these indications, hypothermia must be achieved fast. I think in ischemia, hypothermia should be maintained through the reperfusion phase, and that's true whether we're talking about focal infarction or cardiac arrest. Thirty-three degrees to 35 degrees is the reasonable target range, and mild hypothermia

may be practical for less severely affected patients who are awake. And clinical trials have been encouraging; they have shown safety--the preclinical trials have been consistent, and the clinical trials have been encouraging. They've shown, I think universally, that this is a safely applied approach, and there have been signals of efficacy. But existing techniques for achieving--particularly surface techniques for achieving and maintaining hypothermia are unsatisfactory and new approaches are needed.

Thank you.

CHAIRPERSON CANADY: Thank you very much, D. Grotta.

Ms. Morris, I'm not going to ask you to read the questions. They're so long. But you have the overlays?

DR. BROTT: Jim, do we know--or is there any data that gets at the question of what happens in humans with regard to cerebral blood flow and metabolism when we intubate them, paralyze them, and anesthetize them?

DR. GROTTA: Well, first of all, the cardiac arrest patients, of course, were already auto-anesthetized and intubated. They all were intubated and they received paralytics, and all of the patients were sedated. So what you're getting at is whether there are other factors besides the hypothermia that might be relevant--

DR. BROTT: Well, I'm wondering--

DR. GROTTA: --and the answer is that it's not been systematically studied, though in animals this has been studied, and the metabolic rate is reduced by hypothermia, but it's also reduced by anesthetics. So there is an anesthetic covariant.

DR. BROTT: Well, I guess what I'm--that's kind of the big question, but the measurement question is, you know, with everybody who gets anesthesia, has anybody ever bothered to do PET scans or to look at the effects of anesthesia and paralysis in the human brain?

DR. GROTTA: Well, as you know, there have been studies done of barbiturate anesthesia and other--to see whether that was neuroprotective after cardiac arrest, and it has been shown not to be effective. I don't know about studies in subarachnoid--in aneurysm repair what the studies of anesthetic, propofol and barbiturates, have been, but I don't think they've been a rousing success. Am I wrong--

CHAIRPERSON CANADY: You mean as neuroprotective agents or--

DR. GROTTA: Yes, during aneurysm surgery.

DR. BECKER: I would say just with regards to what cerebral blood flow does with these agents, it depends on the agent in question. It can be increased, decreased, or not changed, depending on your anesthetic that you use. And there have been, actually, some human studies done to look

at that.

CHAIRPERSON CANADY: Other general questions or comments about hypothermia? Or other questions for Dr. Grotta?

DR. HURST: I have one question about the length of time that you can maintain someone. I understand that the complication rate rises after 24 hours. Is this a feasible therapy to think about in vasospasm where we know patients are in clinical vasospasm, in many cases for days at a time.

DR. GROTTA: Well, in the head trauma study, patients were kept hypothermic for several days so, yes, but the complications do go up, particularly the cardiovascular complications of hypotension and in particular the fever--the infection rate really goes up.

But in answer to your question, it could be, and, again, modest hypothermia might be an answer in these patients along with the other measures that are presently already used, like calcium antagonists and whatever.

CHAIRPERSON CANADY: Other questions?

[No response.]

CHAIRPERSON CANADY: Then we'll move on to the first question, which is regarding safety parameters and recommendations regarding temperatures, duration of hypothermia, rate of cooling, rate of re-warming or other

issues that you think would be germane. Comments from the panel?

[No response.]

CHAIRPERSON CANADY: Well, let me open it. It seemed there was a consistent feeling about temperature from all of the speakers that we've heard today in the 32- to 34-degree range. The duration of hypothermia, again, seemed fairly consistent in terms of the conversation of somewhere less than 24 hours.

DR. GROTTA: Well, it depends on the indication. I mean, you know--

CHAIRPERSON CANADY: I understand--

DR. GROTTA: --I think it's difficult to answer these questions for all of the indications. I think you have to take them one at a time, not that I'm trying to prolong this but--

CHAIRPERSON CANADY: No, no.

DR. GROTTA: --I don't think you can really--the target temperature probably varies, as does the duration--

CHAIRPERSON CANADY: What I would recommend regarding that is we're going to in the later question separate them out anyway.

DR. GROTTA: Oh, okay.

CHAIRPERSON CANADY: So we can discuss anything that you think is separate as we approach them in the end.

Under Question 3 we look at each one individually. So I think that's the place for individuation.

Rate of cooling, comments? And rate of re-warming?

DR. GROTTA: Fast. Fast cooling and slow re-warming.

CHAIRPERSON CANADY: Fast, stay there, and come back up.

DR. GROTTA: Right. But I think the rate of re-warming--it's not so much that it has to be so slow, but it has to be controlled. I think that the rebound hyperthermia was probably bad. I don't think we really know what is the optimal rate of re-warming, and I think the reason that we've gone slow is because if you go too fast, then it's hard to stop it and there's frequently a rebound.

CHAIRPERSON CANADY: So that may be, in fact, some advantage of the device.

DR. GROTTA: Yes. Devices, what I've heard today, would promise, it seems to me, to speed the rate of cooling and to control the rate of re-warming.

CHAIRPERSON CANADY: Other comments regarding Question 1?

[No response.]

CHAIRPERSON CANADY: Question 2, temperature monitoring methods--

MS. MORRIS: Could I just ask for a clarification? Can we get any guidance in terms of how long to control re-warming?

CHAIRPERSON CANADY: I think we're going to talk about that again in the separate--

MS. MORRIS: We are? Okay.

CHAIRPERSON CANADY: The sense I had was that it was felt to be different in different diseases. Is that correct?

DR. GROTTA: Well, not so much the re-warming. Generally we went one degree every four to six hours. I think that's the fastest you'd want to go.

MS. MORRIS: But you feel that for cooling it may be different for each--

DR. GROTTA: For cooling, you'd want--I think you'd want to get them down as fast as you can.

MS. MORRIS: Right. Regardless of the indication.

DR. GROTTA: That's right. I think the rate of cooling and rate of re-warming probably doesn't differ. The duration of hypothermia probably does, depending on the indication.

MS. MORRIS: Okay. Thank you.

DR. MARLER: Could I ask if there's any pre-clinical data about the re-warming rate?

DR. GROTTA: I don't know of any.

CHAIRPERSON CANADY: Dr. Witten?

DR. WITTEN: I do have one question, which may be general, there may be a general answer to related to Question 1. I know a lot of it was discussed already in the presentation. But for cooling that is longer than 24 hours, are there any additional safety measurements that should be made in addition to what was already mentioned?

DR. GROTTA: Well, I mentioned a bunch of them in my talk that I think have to be measured no matter what. But I think you're going to get into problems like skin breakdown more frequently with more than 24 hours' duration.

DR. BECKER: Could I also just add that with regard to the last point on the first question, there are specific issues surrounding different technologies, and I think if you're going to do prolonged hypothermia with an indwelling catheter, that might raise a specific problem with regard to thrombosis of that catheter. Some of these catheters are quite large and have very irregular surfaces. So I think that's going to be one particular safety concern.

CHAIRPERSON CANADY: Other questions?

[No response.]

CHAIRPERSON CANADY: We'll go on to No. 2, the recommendations for temperature monitoring. I think the first one was brain versus core temperature, and then I imagine there could be a number of different sites to

manifest core temperature. Any thoughts from the committee on that?

DR. WOZNER: I think the research is pretty clear about core temperature monitoring, and that either pulmonary artery catheter or bladder temperature are considered the gold standard.

CHAIRPERSON CANADY: Other comments or disagreement?

DR. GROTTA: I would agree. You certainly don't want to measure anything close to the periphery because that's going to be affected by blood shifts and--we used bladder temperature in our cardiac arrest trial, but I think pulmonary temperatures would be fine.

DR. BECKER: I didn't hear anything presented today about just cooling the brain as an isolated organ. I know that there are technologies that exist for that, and that would raise a different set of monitoring standards because you wouldn't be targeting global hypothermia or core body temperature would not be an accurate assessment of what's going on.

CHAIRPERSON CANADY: There is, in fact, underway now a hypoxic ischemic brain protocol by the neonatology group, experimental group, looking at hats, putting on cooling hats. So that would represent a different issue.

The third question goes--really divides into the

different disease entities, the first one being cardiac arrest patients. In looking at the same issues, the first one would be inclusion/exclusion criteria, safety parameters, outcome measures, primary and secondary effectiveness outcomes, and what would be the appropriate control population. So the floor would be open to comments, questions, thoughts on this issue--issues, really. What about--let's start inclusion/exclusion, so you don't feel overwhelmed, criteria.

DR. GROTTA: Not to be redundant, since I just gave the talk, I think that we tended to be very conservative initially in the sorts of patients that we put in, and I've been struck by--and I think those other studies that have been done in cardiac arrest, given the fact that these are patients who've had obviously an awful thing happen to them, surprisingly have very few complications during the hypothermia period of 24 hours. So I don't think we have to be that exclusive. I think we can take inpatient arrests, outpatient arrests. I think we can take patients with myocardial ischemia. We even can take patients who go to the cath lab, who need to go to the cath lab for rescue, angioplasty, or stenting. There's no reason why those patients also can't be made hypothermic.

So I would--I think that coma isn't--obviously you don't want to cool somebody who's already waking up because

they have a good prognosis, but I think persistent coma--I think that you do need to have a cut-off for blood pressure, the patients have to have a reasonably stable blood pressure indicating that they've been resuscitated adequately. If they have to be on large doses of pressors in order to support their blood pressure, that probably means their downtime was very long or their cardiac function is so long that their prognosis is--that they're probably unsalvageable.

CHAIRPERSON CANADY: Yes, Dr. Marler?

DR. MARLER: I would agree with that, but more on a theoretical basis in that with early studies it's very difficult to predict which subset of patients is going to respond best to your therapy. And I would just suggest, unless there's a well-documented reason for excluding someone related to safety, then I wouldn't--you know, just strive to exclude as few patients as possible in early studies so that you can, you know, let--so you can discover who's going to respond most. Often it isn't the subsets you'd predict initially.

CHAIRPERSON CANADY: Dr. Zivin?

DR. ZIVIN: Just to add to that, considering how bad the statistics are on resuscitation of these patients, successful resuscitation, and even resuscitation to survival isn't necessarily a good thing, but I think that these

people really have anything that would potentially benefit them is a reasonable thing to try.

CHAIRPERSON CANADY: Dr. Brott?

DR. BROTT: I had a question with regard to--with this issue that John says, which I agree with completely in general terms to keep it wide. On your exclusions in the one trial that you mentioned, could you just mention--you've got a return of spontaneous circulation restriction of 60 minutes. You've got a Glasgow Coma Scale of 8; with the latter, of course, the patient's got to be comatose. But with those two exclusions, are either one of those widenable? What was the experience there?

DR. GROTTA: Well, if a patient's had an arrest and is waking up, then I think their prognosis is very good, and generally I don't think that--I mean, I guess you could include those patients, but--

DR. BROTT: If it's 9--

CHAIRPERSON CANADY: Microphone, please.

DR. GROTTA: We don't have data on patients with Glasgow--let me just say that there are two very large trials that are going to be reported in the next few months, one from Europe and one from the Pacific area, which have large numbers of patients which have been cooled and have control groups, and probably from that study we'll learn quite a bit more about subgroups that might benefit. Maybe

all of them benefit, but we'll probably learn a lot more than what I can generate from just these few numbers of patients. I'd be very loath to make any real strong recommendations from this study other than the fact it seemed to be very safe and there's a suggestion that, you know, some people wake up.

So I would right now say you should keep your inclusion criteria very wide and wait and see what these other studies show.

CHAIRPERSON CANADY: Under the second component of that, safety parameters, we've discussed heat, cool-exacerbated diseases. Other factors people would like to put there? Would we want to put a parameter of the degree of cooling at this point or leave that open as well?

DR. GROTTA: Well, I mean, these patients have nothing to lose from cooling them down to 33 degrees. They're already comatose, and we know preclinically that the cooler, the better. So as opposed to a patient who's already awake, like a mild stroke patient, there seems little reason not to cool them to 33 degrees.

As far as safety, the only thing I'd point out is we did see status epilepticus in four patients, and this hasn't been reported in other small trials of hypothermia, but I think that's something to look at, whether--maybe you're salvaging some neurons that would otherwise die, and

in patients who are coming out of their arrest, they may have a more irritable brain and have a higher incidence of seizures. It's something at least to keep in mind.

CHAIRPERSON CANADY: Any other--

DR. BROTT: One comment I had on the inclusion is, as somebody who is married to a spouse with Raynaud's disease, you know, I would hope that she would not be excluded from any trial.

[Laughter.]

DR. BROTT: So I do think that we have to keep in mind in the exclusion of these thromboangiitis obliterans, Buerger's disease, you know, the risk to them from that disease versus the risk to them from head injury, cardiac arrest, and so forth.

CHAIRPERSON CANADY: Very good. Are there--

DR. GROTTA: I'd just like to reiterate my plea for possibly deferred consent in these--waivered consent in these patients. It's very difficult--these are obviously people, particularly that of hospital ones, who are picked up on the street usually without somebody with them who knows them and is able to give consent. And with time being an issue, I think just as with the head injury trial, waiver of consent is something to think about.

That may be difficult when you're talking about a new device. But I think it is important if we're going to

get the treatment started fast. And we could have doubled the number of patients that we enrolled had we been able to do a waiver of consent.

DR. MARLER: I know one thing on exclusion criteria, thinking back, that wasn't addressed was really the issue of what about the patients that come in already cool. And I know there's quite a bit of confusion because I think there have even been trials when they considered warming those patients that were randomized to the non-hypothermic group. And for what it's--I don't have any particular opinion, but I know it certainly makes it confusing to know what to do with those patients.

DR. BECKER: I guess in the cardiac arrest situation there's data that exists that people who already come in cool do worse, probably reflecting a prolonged downtime more than anything else.

DR. GROTTA: That's right. In trauma, the colder they came in, the better their outcome, because probably they were cool and they got cooler early after their trauma and, therefore, maybe they were made hypothermic sooner. But in our cardiac arrest trial, at least so far, Kyra's right, the patients that came in very cold did worse because--we think because they probably were dead--deader.

CHAIRPERSON CANADY: Yes?

DR. WOZNER: I think the only thing that I might

add in terms of safety measures would be it would seem to me that if you're going to have a very wide net of inclusion for these cases that you'd want to follow some form of left ventricular function in each of these cases, because it's likely that you're going to have to stratify your findings into certain groups based on that function if you're going to have any meaningful data. So things like pulmonary artery catheters, ST segment monitoring continuously, things like that I think would be very valuable in this population.

CHAIRPERSON CANADY: As a data collection tool. Outcome measures?

DR. GROTTA: Let me just say something about the pulmonary wedge pressure. We were concerned about that because we were afraid that if hypothermia made the heart more irritable and we put a swan in a patient when they were cool, that this might be a problem. It hasn't proved to be a problem so far, but it also hasn't proven to be necessary; at least in the 24-hour cardiac arrest patients, we just didn't get into trouble with shock or significant arrhythmias. But if needed, it certainly could be done.

I certainly think that's true with more prolonged hypothermias, like if we're going to do it for several days.

CHAIRPERSON CANADY: Other comments? Dr. Fessler?

DR. FESSLER: I don't know if this is an appropriate comment or not, but in response to your comment,

Tom, for a clinical trial I would strongly argue for the exclusion of patients with diseases such as Raynaud's and thromboangiitis obliterans, et cetera, because there's no question in my mind that if you were lucky enough to save that patient and they lost their fingers, you would have an indefensible several-million-dollar lawsuit.

CHAIRPERSON CANADY: Although we can't practice medicine for the lawyers.

Other comments about that? Can I have some comment on outcome measures? Alive? Awake? Anything more sophisticated?

DR. HURST: You know, it sounds like that alive is certainly a good thing. Cognitive evaluation at one month maybe with neuropsych testing particularly directed toward memory function would be a good thing to look at.

DR. ROSSEAU: I would agree, but I would say that if it's done at one month, it needs to also be repeated at six months probably at least, and perhaps farther out than that.

CHAIRPERSON CANADY: Other comments? Yes?

DR. EDMUNDSON: I would think in this setting, as well as the previous setting of endovascular devices for acute ischemia, that some of the current scales that we have need to be relooked at and probably fine-tuned for folks who have a lesser level of deficit, because that's more

important on the recovery side, and that is underscored here where you have global ischemia or hypo-perfusion that there are neurobehavioral effects and they're individuals who have dyspraxias and fine motor deficits. So if they survive and they're able to ambulate, a Modified Rankin Scale does a really poor job of defining whether or not their quality of life is improved enough to be employed.

So probably we should think of some standard parameters for all of the different study groups that we're considering today. For example, does a patient have a job six months out? That's one thing. Folks who are aphasic, folks who have dyspraxias in the neurobehavioral effects, the Modified Rankin Scale is quick, simple, and probably a good baseline when you're dealing with a three-hour window. But in follow-up, we need other parameters to measure fine motor skills and so on and so forth.

CHAIRPERSON CANADY: So we could perhaps put that in the primary and secondary effectiveness?

DR. EDMUNDSON: Right.

DR. GROTTA: There was a whole battery of neuropsych tests that were done in the head injury trial. When that's reported, there will be a huge amount of data on the outcome of those tests after cardiac arrest--I mean, after head trauma.

CHAIRPERSON CANADY: Any other comments on primary

and secondary effectiveness data?

[No response.]

CHAIRPERSON CANADY: Control population? Cool, not cooled? Yes. Okay.

Any other comments about cardiac arrest in any regard relative to--

DR. GROTTA: I would just re-emphasize the point I made, though, during my talk that with cardiac arrest, the landscape is changing considerably with AEDs. So outcomes are improving, and you have to have a control--a randomized, non-hypothermic control group and can't rely on natural history data. I think that's true of all of these, but particularly in cardiac arrest.

CHAIRPERSON CANADY: That seemed to be the consensus of the panel.

We're going to move on then to traumatic head injury with the same view, look at inclusion/exclusion, safety, outcome effectiveness, control population, and then also the addition of pediatric patients in this one.

Any comments about hypothermia in traumatic head injury relative to those issues? Just in general first. Dr. Marler?

DR. MARLER: I don't know if it would be useful, but I think that if it would save time, that randomization without consent--I forget the exact term for it--waiver of

consent certainly would seem to be advisable if it saved time to treatment.

CHAIRPERSON CANADY: Seems to be consensus on the panel for that, is it fair to say, or not?

DR. ROSSEAU: There's also with trauma patients going to be the obvious fact that a number of them will be alcohol and other drug intoxicated, and I would not make those exclusion criteria by any means, but I would require separate analysis of those groups.

CHAIRPERSON CANADY: So cohort group--

DR. ROSSEAU: Yes.

CHAIRPERSON CANADY: Other comments?

DR. KU: One comment on the characteristics of the control population. Since this is a trauma group, you may want to consider the severity of trauma to other portions of the body in addition to the head, because that may affect the outcome of the patient.

CHAIRPERSON CANADY: It makes sense.

Other comments?

[No response.]

CHAIRPERSON CANADY: In terms of outcome measures, any difference in timing relative to, say, what we suggested for--really, in terms of outcome measures, we really need to establish them for this, or at least make recommendations. Alive's probably not enough.

DR. GROTTA: I was surprised in the cardiac arrest--that patients that we--in our study, they either died or they lived, obviously, and the ones that lived within a week were pretty much back to normal and didn't really change much. I think with the main effect with cardiac arrest you're going to see within the first week to a month. I don't think you need prolonged measures in cardiac arrest. With head trauma, that's not the case. With head trauma, these patients, as you know, they sort of linger and they take a long time for things to sort out, and there can be a delayed recovery up to six months. So I think that you need a more prolonged outcome measure in those patients.

CHAIRPERSON CANADY: So we're looking at time measures up through six months. Is that--

DR. GROTTA: That's, again, what was used in the head trauma trial that was done in the multi-center trial that I reported, and I think that that's been the observation of the investigators, that there was improvement through that period of time.

CHAIRPERSON CANADY: Other comments regarding that?

DR. BROTT: I would just comment that, for Jim's first point, if there's good neuropsychological data to show that that's the case, you can go very quick with the post-

cardiac arrest patients. I think that's fine. But there may not be such data at this point, and if there isn't, then I think that, you know, higher functions in general, with stroke, anyway, we know take quite a while. And we would need data to be certain that early assessment would be valid before we could really accept that.

CHAIRPERSON CANADY: Dr. Zivin?

DR. ZIVIN: Yes, I think it's premature to be deciding anything about what psychometric or other sorts of endpoints ought to be established for these types of trials. I simply don't think we have enough data right at the moment, and that should be open for further discussion at the time when the thing comes to evaluation.

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: I think the decision you have to make at this point, if you're going to include psychometric data, is: Are you willing to make the decision that if the psychometric data is bad for the group of populations you treat with hypothermia, then are you going to deny hypothermia as a treatment to save life? That's the decision you have to make; otherwise, psychometrics at this point don't make any difference.

CHAIRPERSON CANADY: Other comments? Control--

DR. GROTTA: Well, in the cardiac arrest patients, remember, the parts of the brain, as you know, that are

affected are very prominently associated with memory and cognition. And so you can have fairly striking cognitive abnormalities and have someone that looks otherwise fairly normal, and those are devastating deficits. And I think that even if someone would--maybe you wouldn't want to withhold it, but I think it is relevant to know whether somebody survives to be intact or survives to be otherwise severely incapacitated from a cognitive standpoint.

CHAIRPERSON CANADY: Maybe some of that falls back into our primary and secondary effectiveness with the various functionality scales that we've discussed today. So the data should be collected in that regard.

Any other comments regarding control? Yes? No? No comments? Yes.

Pediatric considerations, any additional thoughts?

DR. HURST: Is there any reason to think that it's different in pediatric patients or an age cut-off or something like that?

CHAIRPERSON CANADY: Not from the data available. I don't think there's much data available.

DR. FESSLER: Just from a public health standpoint, I mean, I would think that you would want to do a study in kids. Trauma is, what, the leading cause of death in children.

CHAIRPERSON CANADY: Yes.

DR. FESSLER: And it would seem to me that here's an opportunity to push the issue of inclusion of children in randomized--in trials.

DR. HURST: If pediatrics follows the pattern that they have in every other field, we would expect our best results there.

CHAIRPERSON CANADY: Well, the outcome in head injury is so much better in general.

DR. GROTTA: And in the head injury hypothermia results, the younger patients seemed to respond better even than the adult population.

CHAIRPERSON CANADY: Other comments regarding head injury? If not, we'll move on to stroke. And the same questions, inclusion/exclusion, safety parameters, outcome measures, primary and secondary effectiveness, and controls. The floor is open to questions or just general comments in this area.

DR. GROTTA: I think that really everything has been said about stroke by Dr. Zivin and earlier. The only distinct things I'd say about hypothermia is that I really do feel that modest hypothermia--that we have an opportunity to consider using hypothermia to 35 degrees as a therapeutic modality that could be done in awake patients. I really don't think that it's appropriate to sedate, paralyze, and intubate awake stroke patients in order to deliver

hypothermia. I think that--and most stroke patients, 90 percent of them, as you know, come in and are awake, have Glasgow Coma Scales above 9 and will not tolerate being awake to temperature below 35.5.

But that doesn't mean there isn't an advantage to lowering temperature to that level, particularly in combination with other therapies, and this is one situation where I think that invites combination--evaluation of combination therapies, where you may be able to amplify the effect of another neuroprotective drug with early administration.

DR. FESSLER: The only complication that I can see with this is in the probably rare circumstances where you might consider doing hypothermia along with thrombolysis, because it is established that lowering temperature does decrease thrombolysis rates, but I'm not sure to what extent that would actually be an important issue in a clinical trial where patients are unlikely to be hypothermic very rapidly and the thrombolysis is over fairly quickly.

DR. GROTTA: This actually has been looked at, and like any enzymatic process, it is slowed a little bit by hypothermia, but there was no in vitro, I believe, studies--or in vivo also. There have been in animal models. I don't think there's been any increase incidence of bleeding or other complications of hypothermia in combination with tPA,

though those studies need to be done--more of such studies need to be done. I would be--I don't think that it's going to turn out to be a big issue.

And Dr. Krieger reported their results where all those patients got thrombolysis, and I think the number's probably too small to say for sure, but I don't think they felt like there was an increase in complication rates.

CHAIRPERSON CANADY: Outcome measures? Three months, six months? Same.

Primary and secondary effectiveness would be the functionality scales. Anything else?

Control population, yes? Yes?

DR. BROTT: I'm still a little confused on the inclusion/exclusion in that, you know, if we don't study stroke patients, unless they're not awake, of course, we're not really going to be studying very many. And I didn't hear a resolution there in terms of--for instance, Dr. Krieger's cut-off I think was NIH Stroke Scale score of 20. Is he still here?

DR. GROTTA: No.

DR. BROTT: Was it not?

DR. GROTTA: You're right. I mean, I agree. I think that a study would have to be--what I said when I gave my talk, I would dichotomize it. If the patients come in with a malignant middle cerebral artery syndrome and, let's

say, a NIH Stroke Scale score of 15 or more with the right hemisphere or 20 or more with left, then that patient I think you could justify--and has other criteria predictive of malignant middle cerebral syndrome, then I think that patient you could justify perhaps intubating and sedating and giving more moderate hypothermia to 33 degrees. If they don't meet those criteria, then I would cool them to 35.5 degrees and leave them awake.

CHAIRPERSON CANADY: Other comments? Dr. Edmundson?

DR. EDMUNDSON: It's still unclear. If you include patients who have proximal carotid occlusion, for example, pretty large hemispheric infarct, I think it has to be explicit that interventional measures probably would be excluded if they're going to have hypothermic therapy. Right?

DR. GROTTA: No. Not necessarily. I mean, if it becomes--if that's an approved effective therapy, then there's no reason why that shouldn't be--it couldn't be used. As I pointed out, the cardiologists feel perfectly comfortable taking patients to the cath lab and stenting them, their hearts, and in a hypothermic patient. So if it were shown, for instance, that intra-arterial thrombolysis were effective and that became a standard of care, there'd be no reason, I would think, to exclude such patients from a

hypothermia trial.

DR. EDMUNDSON: But are we there yet? I mean--

DR. GROTTA: No, there--

DR. EDMUNDSON: --if you're for having investigations about doing those studies, then you ought to exclude those folks until the studies--

DR. GROTTA: Yeah, I think that unless it's specifically part of your study design, I think you always want to stick to one experimental intervention. I do think, though, as I pointed out, that with neuroprotection it might--this might be a way, though, to test two experimental therapies if we could figure out a valid statistical and regulatory way to do it, because I do think, as I said, hypothermia's a good--would be a good candidate for such a combination.

CHAIRPERSON CANADY: Dr. Marler?

DR. MARLER: I don't think patients should necessarily be excluded from an acute stroke hypothermia trial because they're eligible to receive tPA.

DR. GROTTA: If they're eligible for routine tPA.

DR. MARLER: Routine, yeah.

DR. GROTTA: He was talking, I think, about intra-arterial--weren't you? I mean, if the patient--

DR. MARLER: I missed it. Sorry.

DR. GROTTA: But if they're going to get IV-tPA

within three hours, then they would go in.

DR. BROTT: Could I ask, how do you monitor for intracranial hemorrhage? If, you know, a patient comes in within three hours, you give them IV or maybe you give them IA, and then you paralyze them, intubate them, and put them in hypothermia, so you don't have any focal signs, what should we do to--or what should we advise for monitoring? Do you do EEG monitoring? Do you do CTs? Because you've got maybe a rise in blood pressure, your cues for, you know, asymptomatic hemorrhage are kind of attenuated.

DR. GROTTA: Well, you'd have to ask Dr. Krieger what they did because they did the study. That's exactly what they did. They took patients who had bad strokes, and they gave tPA to and made them hypothermic. So I don't know what--I don't think they're here anymore, so I don't know what their monitoring algorithm was, but it would seem to me you would have to have frequent--maybe two CT scans during the--

DR. BROTT: Well, I do recall he said they had one hemorrhage, and it was picked up on the--as I recall, it was picked up on the 24-hour CT scan. But, of course, you know, most of them are occurring the first 8 to 12 hours after you give the drug.

DR. GROTTA: Of course, as you know, there is no recognized effectiveness therapy for the hemorrhage if it

occurs, anyway, so I'm not sure that recognizing it is going to make a difference in the outcome. Maybe the best thing you could do is to have that patient hypothermic when they bleed. Right?

[Laughter.]

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: Perhaps the other neurosurgeons on the panel can comment on this, too, but I would say you have no alternative--no alternative other than to put an intracranial pressure monitoring device.

DR. : In every patient?

DR. FESSLER: Yes. Every patient that's intubated and anesthetized, yes.

DR. GROTTA: With large focal stroke. I don't think with cardiac arrest you need to do that, but I think that's a reasonable thing to consider.

CHAIRPERSON CANADY: And it's relatively risk-free. But invasive.

Other comments?

[No response.]

CHAIRPERSON CANADY: Primary and secondary effectiveness would be the functional scales. Anything else?

[No response.]

CHAIRPERSON CANADY: Control population, yes?

[No response.]

CHAIRPERSON CANADY: Any other comments about stroke in general before we move on?

DR. EDMUNDSON: Just one comment about cooling a patient on Demerol, because, you know, we're dealing with patients who have cortical irritability from stroke or from ischemic encephalopathy. So in the setting of hypothermia, a lot of metabolic processes are slowed. The Demerol metabolite, normeperidine, is neurotoxic, and incidence of status epilepticus would be increased probably quite significantly. So using that in preparation as one is cooling a patient and they're shivering before he can intubate them, paralyze them, probably should avoid Demerol.

CHAIRPERSON CANADY: Yes, Ms. Maher?

MS. MAHER: I just have one comment, and it's a more general comment on stroke and control patients in stroke. I've gotten a lot of comments and seen a lot of instances where people are saying when they're trying to do controlled studies with stroke patients, they can't get people to be involved in the studies because the doctors do not want to have a control arm where they're just doing the medical treatment, which is in many cases nothing. So I think we as a group need to be very careful when we sit here now, this afternoon and this morning, having said we want control patients, to allow the FDA and industry to have the

opportunity to, where there's not going to be the opportunity to enroll control patients, to expand the study to something else as well. So we just need to keep that in mind.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: Then let's move on to aneurysm surgery. The concept I think you understand now. Inclusion/exclusion, safety, outcome measures, primary and secondary effectiveness, control populations. General comments or specific comments on this issue?

[No response.]

T7A CHAIRPERSON CANADY: Any groups that you feel should be excluded from a trial of aneurysm surgery?

DR. GROTTA: Well, again, the preliminary results, the patients who bled with aneurysms, not those who are having aneurysm surgery who hadn't bled, so, again, that would seem to be a target group, and the only other thing I took away from the trial of groups that should be excluded were that, at least with external cooling, they couldn't cool obese patients. But that may not be a problem with intravascular catheters.

CHAIRPERSON CANADY: Safety parameters?

DR. WOZNER: I think the only thing I would add is that there's a growing body of evidence that aneurysm cases

oftentimes do suffer from left ventricular changes related to ischemia, in particular, and I think that's something that you'd have to monitor pretty closely when you're combining this therapy with traditional measures such as HHH therapy.

CHAIRPERSON CANADY: Maybe we can put that under primary and secondary effectiveness measures.

Other comments? Dr. Marler?

DR. MARLER: I was thinking that the subarachnoid patients do get a lot of other therapies, with calcium channel blockers--do they still get that?--and the--

DR. GROTTA: But these patients were just cooled intraoperatively so that it's not like--

DR. MARLER: That's right. Everything else is pretty well controlled with--

DR. GROTTA: Well, I mean, nimodipine is started, and they may be on nimodipine even if they--even preoperatively if they're good grade patients. But I guess the point is that we're not talking about prolonged--usually not talking about prolonged hypothermia, at least in the trials that have been postulated so far.

Now, in vasospasm, if you're going to use it to treat vasospasm for several days, that's another issue because then you do have all these other therapies, like angioplasty and hypervolemic therapy that could be

confounding factors. So it's different whether you're just talking about intraoperative hypothermia or hypothermia for vasospasm.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: Outcome measures in this group? Particularly if we're talking about aneurysms that bled, that becomes a little complex, I think.

DR. : Aren't cognitive measures also very important in this group?

CHAIRPERSON CANADY: Control group here?

DR. GROTTA: Again, I think that--I don't know what--I don't know that Dr. Ogilvy's still here, but the measures are--what they are measuring in their trial, but good outcome, I think Glasgow Outcome Scale and things like that were the main--and cognitive measures and neurological deterioration in the hospital, probably from vasospasm, were the main measures that were looked at.

CHAIRPERSON CANADY: Other comments?

DR. BROTT: I just had one question that I guess is to Dr. Fessler or any of the neurosurgeons. You know, recently the morbidity and mortality from the unruptured aneurysm study was a little higher than any of us wanted it to be. And then some follow-up--there was a follow-up paper, as you know, on imaging in the New England Journal

where, again, the morbidity was higher with the unruptured group than, you know, any of us want it to be. And I would presume that maybe some of these studies with unruptured were done a little bit earlier with hypothermia, and I'm hopeful that surgery for unruptured aneurysms could be improved. Is this an area that we should just say is not open to hypothermia, surgical operation on unruptured aneurysms?

DR. ROSSEAU: I would not think so. I'd be interested in hearing what the other neurosurgeons say. I think there are two distinct questions that you raise. One is why are patients who are being operated upon for unruptured aneurysms not doing as well as we would have liked? And, secondly, is there a way we can improve that? But I would not exclude them from any new operative treatment based on that.

DR. BROTT: What I meant was that the hypothermia--hypothermia for that group.

DR. ROSSEAU: No, I would think that might be one way we could improve their operative experience. I would not exclude the unruptured group.

DR. GROTTA: But if you think of the mechanisms by which hypothermia might--intraoperative hypothermia might be effective in a ruptured aneurysm and not in an unruptured aneurysm suggests that it's the anti-inflammatory effect

that might be most important. And, you know, there is presumably no inflammation or little inflammation in an unruptured aneurysm, whereas there is in someone who's just had a subarachnoid hemorrhage. It may be that you're attenuating that inflammatory response.

So, I mean, it's reasonable to speculate that you might not see an effect in unruptured aneurysms, but it's certainly something that should be looked at.

I would also argue that it's worth thinking about hypothermia for intracerebral hemorrhage as well. That's not something on our list of indications. We've studied it in our laboratory, but there's another condition for which there's absolutely no therapy at the present time, where there's a robust inflammatory response, and to the extent that hypothermia reduces that, it might be effective not only in reducing edema but in reducing the inflammatory delayed cell death around hemorrhages. So it's worth adding that to your list of possible orphan indications.

DR. FESSLER: The one place in unruptured aneurysm surgery that hypothermia might be beneficial is in reducing the ischemia, edema, and inflammation secondary to retraction. So that's one place where, in fact, we might be able to see a benefit, and maybe that's the cause of our results not being quite as good as we'd like to see them.

DR. MARLER: Again, I guess I'd urge until there

were evidence to the contrary, you might want to include it. But I don't know.

CHAIRPERSON CANADY: Other comments? Dr. Witten, anything, other directions you would seek from the panel?

DR. WITTEN: Yes, one very important thing that would be helpful for you to comment on, maybe you can go back to the questions, and that's the question about control and looking at the controls, in conjunction with what type of comparison the panel would hope to see in a clinical study, that is to say, or suggest in clinical endpoints. And we've heard a number of comments related to to what extent cooling is or isn't the standard of care. And I think we'd be interested in hearing your views on the appropriate control population for this type of study.

CHAIRPERSON CANADY: I think for an aneurysm study you likely have to compare aneurysm to aneurysm. In terms of cognitive outcomes, they're different based on where the aneurysm's located.

DR. WITTEN: I guess I mean in terms of concomitant treatment that's being offered to the control group. Is this a control group that you're going to use standard methods of cooling and compare that to the experimental method of cooling?

CHAIRPERSON CANADY: Oh, I see what you mean.

DR. WITTEN: Is it experimental--or is it

experimental cooling versus no cooling? You know, are you just going to look at--what type of comparison are you going to make? Or would you suggest that we want to see?

DR. GROTTA: Are you just talking about subarachnoid hemorrhage? Because I think other than in aneurysm surgery, I don't think that you could consider hypothermia a standard of care in anything. So I don't think it's--

DR. WITTEN: No, I mean particularly in aneurysm surgery.

CHAIRPERSON CANADY: My sense is that the current method of cooling is felt to be very unreliable, widely variant, and not very much in control. So I think that one would want to monitor the temperatures, but I'm not sure that I would create a model of cooling based purely on external cooling versus whatever new modality there may be. What are the panel's thoughts?

Come on. It's not even 5 o'clock yet. You've got to still have thoughts.

MS. MAHER: It seems to me, if you're talking about the control being the normal standard, you would want to cool it the way you normally would versus the treatment group. But I think you will have problems once you have a few successes with the treatment group, feeling that you want to continue to control it in a way that's less

reliable.

CHAIRPERSON CANADY: Well, to me, I guess I would go back to the concept that cooling's not the standard of care for anything. So why would we make that a control group?

DR. GROTTA: What if you--to get away from this, if surgeons are uncomfortable not cooling their patients, why not just cool all patients and look for a dose response relationship. You do enough patients and you look for better outcome in 33-degree patients than 34-degree patients, better than 35. I mean, if you saw a dose response, wouldn't that be convincing that hypothermia then is effective?

DR. WITTEN: Well, we're really asking you, so I appreciate the suggestion.

DR. GROTTA: The answer would be yes. In my mind, it would be convincing.

[Laughter.]

DR. GROTTA: And it would get away from having to have a control group.

CHAIRPERSON CANADY: Anything else, Dr. Witten, you'd like help with that we--

DR. GROTTA: I'd like to say one other thing I forgot to mention on the infarct, which is a confounding issue and I think will turn out to be a confounding issue,

is the hemicraniectomy issue. One reason why I think that we shouldn't focus just on the malignant middle cerebral artery syndrome patients for our infarction studies is that there's now a trial going on of hemicraniectomy in these patients, and so when you think of confounding therapies, that would be a very difficult one to control for. Many of these patients--many people who have a hard time--there's been statements in the literature that it's unethical to randomize patients who have malignant middle cerebral artery syndrome to hemicraniectomy or non-hemicraniectomy, that they all should have it. I don't think that's necessarily the case, but it's important to keep in mind when these studies come before you that that's a therapy that's often carried out in the same group of patients.

CHAIRPERSON CANADY: Other comments? Any general comments people would like to make?

Dr. Witten?

DR. WITTEN: I'd just like to thank the panel and the public for their participation and the FDA staff for their assistance and preparation.

CHAIRPERSON CANADY: We will then close this session of the panel. Do you have a comment? You're not on the panel. He's an FDA guy? Is he an FDA guy?

VOICES: No.

CHAIRPERSON CANADY: Then you can't make a

comment. Sorry.

DR. DIRINGER: I had a question. Is that allowed?

CHAIRPERSON CANADY: No. Oh, are you a speaker?

DR. DIRINGER: Yes.

CHAIRPERSON CANADY: Oh, come back. I'm sorry.

[Laughter.]

DR. DIRINGER: Maybe it's an observation. I'm not sure. But it seems that we have--oh, Michael Diringer. I participate in a study with Alsius on fever control. I have no financial interests in any of these devices or companies.

We seem to be intermixing the effect of a therapy, i.e., hypothermia, with a device to induce hypothermia. And the questions are intimately related but really different. And I find that this is a little bit confusing for me as an outsider to understand how people should approach this.

We have a therapy--hypothermia. Does it work or doesn't it work? Which is really in some ways independent of how you achieve it and whether a particular device does it or doesn't it. So is there some way we can address does hypothermia work and then manufacturers will have to demonstrate that they can achieve hypothermia safely and effectively.

CHAIRPERSON CANADY: I understand how you get that confusion. I think the panel's speaking as people who will receive the second set of data also. We have discussed that

in the course in the conversation today. But I think we at the very end separated those issues out in terms of hypothermia. How you get there may not be the issue in terms of the design, and whether or not--how you got there may not be the appropriate control.

DR. DIRINGER: I think we need to revisit what the control groups ought to be again.

CHAIRPERSON CANADY: Okay. We can do that. Comments from the panel?

DR. GROTTA: Well, in other words, what you're--

CHAIRPERSON CANADY: He's suggesting the question is--

DR. GROTTA: --saying is--

CHAIRPERSON CANADY: What is the appropriate control groups?

DR. GROTTA: If you have a patient who you're trying to achieve hypothermia using a catheter, do you need to use cooling blanket hypothermia as an appropriate control group?

DR. EDMUNDSON: Or should it be stratified to cooling and no cooling?

DR. HURST: It seems you could do either one. It depends on the question that you're trying to answer. If you're marketing a device whose intent is to drop the temperature quickly, maintain it within a very narrow range

and then bring it back up at an appropriate rate, and that's what it's designed to do, then you would want to use as a control group whatever the current method of inducing hypothermia is, and you may not want to say anything about the clinical outcome.

DR. GROTTA: But as I see it, I mean, hypothermia with a cooling blanket is hypothermia using a device. Why would you need to show that one device--and it's not approved for purposes--any of the indications that we're talking about at the present time. So why would you ask a new device to be superior to another device that's not approved?

CHAIRPERSON CANADY: I think one wants to assess the effectiveness of whether you achieved hypothermia, at what temperatures with what range over what time, and then based on that, the effectiveness of the therapy.

DR. MARLER: I guess I want it to be clear. I don't think I would be comfortable, at least at this early stage, using temperature as a surrogate the same way you d recanalization for thrombolytic therapy. I mean, just to get the patient to a temperature, I mean, surrogate for what? None of the studies have shown that the temperature lowering works at all.

CHAIRPERSON CANADY: I mean, there are two different--again, that's back to the gentleman's question of

separation of issues. One is how do you accomplish hypothermia and did you successfully accomplish hypothermia with your device? The second is: What is the clinical efficaciousness of that temperature? And they're not exactly the same issue.

DR. BROTT: And for such studies, I would agree with you and Dr. Grotta that since we don't have a gold standard, to create a quasi-gold standard for comparison would sacrifice the patient's ability to contribute to the public health because you would be diluting the power of your study.

DR. BECKER: The first and most important question to answer is whether hypothermia is effective. Once you answer that, then you can look at devices and how they get there, but that's not the important question right now. It's is hypothermia an effective treatment, period.

CHAIRPERSON CANADY: Other questions?

[No response.]

CHAIRPERSON CANADY: To our questioner, does that answer his question?

DR. DIRINGER: Yes. Thank you very much.

CHAIRPERSON CANADY: You're welcome.

We will then adjourn.

[Whereupon, at 5:00 p.m., the meeting was adjourned.]

CERTIFICATE

I, **SONIA GONZALEZ**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

SONIA GONZALEZ